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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,822	03/19/2004	Lawrence W. Stanton	135/003P	7106

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,822	STANTON ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-26* is/are pending in the application.

4a) Of the above claim(s) *22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-7-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 2-28-07 has been entered. Claims 1-20 have been canceled. Claims 21-26 have been added.

Newly submitted claims 22 and 23 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 22 and 23 are drawn to non-elected subject matter, i.e. group II in the Restriction Requirement mailed 8-18-06, in which group I is the elected subject matter.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 22 and 23 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 21-26 are pending. Claims 21 and 24-26, and measuring PODXL expression at protein level, are under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 21 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention. Applicants' amendment filed 2-28-07 necessitates this new ground of rejection.

Claims 21 and 24-26 are directed to a method for assessing the differentiation of a population of human embryonic stem (hES) cells comprising measuring podocalyxin-like protein (PODXL) expression level in the population of human ES cells, wherein a decrease in that PODXL expression level relative to the PODXL expression level in the population measured at an earlier time point indicates that the population is differentiating. Claims 24 and 25 specify the PODXL expression level is measured at the protein level and by antibody assay, respectively. Claim 26 specifies the PODXL expression level is measured using flow cytometry.

The specification discloses a plurality of marker genes that appear to be more abundantly expressed in undifferentiated hES cell lines when compared to that in differentiated hES cell lines (i.e. differentiated hES cell lines that have been induced to differentiate to embryoid body (EB) formation, exposure to retinoid acid to differentiate to neuronal precursor cells, and exposure to DMSO to differentiate to hepatocyte precursor cells). The specification discloses a plurality of marker genes that appear to be less abundantly expressed in undifferentiated hES cell lines as compared to that in differentiated hES cell lines (Examples 1-3, Table 2 and 3). Examples 4, 5 and 8 demonstrate high level expression of PODXL in undifferentiated hES cells and PODXL expression level decreased after growing the undifferentiated hES cells in unconditioned culture medium by real-time PCR assay (mRNA level).

The claims encompass assessing the differentiation of a population of hES cells by measuring protein expression level of PODXL and comparing PODXL protein expression level to that of an earlier time point. The specification fails to provide adequate guidance and

evidence for how to assess the differentiation of a population of hES cells by comparing PODXL protein expression level of two different time points.

Pera et al., 2001 (WO 01/68815 A1) points out that human pluripotential stem cells express SSEA-3, SSEA-4, Tra 1-60, GCTM-2, alkaline phosphatase and Oct-4 (e.g. p.3). However, there is no evidence of record that shows any two or more of those markers or any marker alone, such as PODXL, would be able to define the undifferentiated state of the hES cells. Mayer-Proschel et al., 2002 (Clinical Neuroscience Research, Vol. 2, p. 58-69) identified multipotent human neuroepithelial precursor cells (hNEPs) and demonstrates that "hNEPs constitute a small fraction of the cells present at any stage examined and three additional dividing populations can be identified based on expression of epitopes recognized by E-NCAM, A2B5 and CD44. E-NCAM+ cells co-express neuronal markers and can differentiate into multiple classes of neurons. Two types of A2B5+ cells can be distinguished: a small neuronal population that co-express E-NCAM immunoreactivity and a larger glial population that is E-NCAM negative. CD44+ cells do not express neuronal markers or oligodendrocyte markers but co-express astrocytic markers and likely represent an astrocyte precursor cell" (e.g. abstract). It appears that there are several different types of neural precursor cells expressing different markers. Differentiated hES cells encompass not only neuronal precursor cells but also numerous different precursor cells or multipotent stem cells including hematopoietic stem cells, follicular precursor cells, and pancreatic stem cells etc. Each precursor cells or multipotent stem cells would also encompass different differentiated stages expressing different markers. The ES, EB, preHEP and preNEU in Tables 2 and 3 of the specification only represent particular undifferentiated and differentiated stages of hES cells. The specification fails to provide specific

guidance for how to use the data provided in Tables 2 and 3 to determine or define numerous different undifferentiated stages, i.e. extent of differentiation, of hES cells and numerous different differentiated stages of various precursor cells or multipotent stem cells. One skilled in the art at the time of the invention would not know how to assess or determine the extent of differentiation of the hES cells by merely detecting or measuring PODXL expression level alone in the population of hES cells.

Further, the data shown in Tables 2 and 3, and Examples 4, 5 and 8 of the specification are expression levels of cDNA rather than protein expression levels. Expression levels of cDNA or mRNA do not necessarily correspond to the expression level of protein since there are post-transcription regulation of mRNA and post-translational regulation of protein. The specification fails to provide adequate guidance and evidence for whether the expression levels of cDNA or mRNA of PODXL gene at different differentiated stages of the hES cells could be translated into expression levels of PODXL protein. Thus, one skilled in the art at the time of the invention would not know how to use antibody assay to assess or determine the extent of differentiation of hES cells as claimed.

The claims recite comparison of PODXL protein expression level with that of an earlier time point. One second, ten second, one minute, ten minutes and one hour earlier etc., are all considered earlier time points. The specification fails to provide adequate guidance and evidence for how different the protein expression level of PODXL would be at those time points as compared to the protein expression level of PODXL at a latter time point. It is very likely that there is no change in the protein expression level of PODXL when those short earlier time points are compared. Therefore, one skilled in the art at the time of the invention would not know how

to assess the differentiation of a population of hES cells by using the claimed method. Further, there is no correlation between the expression pattern of protein via antibody assay and the extent of differentiation of hES cells. The specification fails to provide specific guidance for comparison at what earlier time point, the decrease in protein expression level of PODXL would be statistically significant so that one skilled in the art at the time of the invention would be able to assess the differentiation of a population of hES cells according to said protein expression of PODXL. Absent the specific guidance, one skilled in the art at the time of the invention would not know how to assess the differentiation of a population of hES cells by using the claimed method.

In addition, the claims read on assessing the differentiation of a population of hES cells in vivo. The specification fails to provide adequate guidance and evidence for how to measure the protein level of PODXL, such as via antibody assay, in vivo, whether there would be any difference in protein expression level of PODXL at different time points, and how to assess the differentiation of a population of hES cells in vivo with protein expression pattern of PODXL.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3-7-07 was filed after the mailing date of the non-final rejection on 11-29-06. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER